January 2016

Birth Weight And Risk Of Pediatric Hodgkin Lymphoma: A Population-Based Record Linkage Study In California

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Submitted to the Faculty of the

Yale School of Public Health

in partial fulfillment of the requirements for the degree of

Master of Public Health

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Yale University

2016

Abstract

Objective: To evaluate the relationship between birth weight and the risk of pediatric Hodgkin lymphoma (HL, age at diagnosis: 0-19 years).

Method: We linked California statewide birth records from 1978-2009 and cancer diagnosis data from 1988-2011 to conduct a population-based case-control study with 1,216 cases and 4,485 controls (matched on birth month and year, sex, and race/ethnicity). Conditional logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (95% CI) of pediatric HL overall and by age of diagnosis, controlling for other perinatal factors.

Results: Compared to children with a normal birth weight (2500-3999 g), those who had a high birth weight (≥ 4000 g) had a significantly increased risk of pediatric HL overall (OR=1.23, 95% CI: 1.02-1.48). The magnitude of association was larger for subgroups of children whose age of diagnosis was 0-10 years (OR=1.56, 95% CI: 1.04-2.24) or 15-19 years (OR=1.43, 95% CI: 1.11-1.83), while no association was observed in 11-14 year olds. Compared to firstborn children, those who were third or higher in birth order had a significantly reduced risk of pediatric HL overall (OR=0.80, 95% CI: 0.67-0.95), and this association also varied by age of diagnosis.

Conclusions: In this study with the largest number of pediatric HL cases, high birth weight was associated with an increased disease risk. The different findings by age of diagnosis regarding both birth weight and birth order underscore the importance to stratify pediatric HL by age at diagnosis in future etiological investigations.

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Introduction

In the United States (US), Hodgkin lymphoma (HL) is the third most common pediatric malignancy, accounting for approximately 4% of cancer diagnosed in children 0-14 years of age.[1] The incidence of HL is higher in adolescents (3.0 cases per 100,000 person-years among ages 15-19 years in contrast to 0.6 cases per 100,000 person-years in children aged 0-14 years), among whom HL is the most commonly diagnosed malignancy and represents about 15% of cancer diagnoses in this age group.[1,2] In 2014, there were a total of 1,140 estimated new cases of pediatric HL (age 0-19 years) in the US.[1] Although survival rates are now extremely high due to improved treatments, pediatric HL survivors retain elevated risks of treatment-related morbidities over the long term, which can severely impact quality of life.[3] The etiology of pediatric HL is not well understood, and research in this area remains a high priority.

Recent epidemiologic investigations have evaluated various perinatal characteristics for possible associations with pediatric HL. In particular, birth weight has been assessed in several of these studies as a potential marker for intrauterine growth, with inconsistent results. Multiple studies[4-11] and a meta-analysis published in 2012[12] found no association between birth weight and risk of pediatric HL. However, a large birth cohort study from Sweden observed a significant positive association between high birth weight and risk of HL in cases diagnosed under the age of 15 years, as well as those diagnosed at the age of 15-37 years.[13]

Two factors could have contributed to the inconsistent findings. First, given the rarity of pediatric HL, most existing studies included a relatively small number of cases and likely had suboptimal statistical power. The number of HL cases in the studies included in the meta-analysis[12] ranged from 84 to 474, while the Swedish birth cohort study included 943 HL cases.

Second, different studies included HL cases who were diagnosed at different ages, with many focusing on HL cases diagnosed at the age of 0-14 years.[4-6,8,10,11]

Given the high incidence of HL at the age of 15-19 years[1] and the lack of consensus on the relation of birth weight to the risk of HL, we designed a population-based record linkage to conduct a large case-control study with an unprecedented sample size in order to clarify the role of birth weight in the etiology of pediatric HL, with a particular emphasis on covering the entire range of age of diagnosis (i.e., 0-19 years).

Methods

Study Design

We linked California statewide birth records from 1978-2009 (maintained by the Vital Statistics Division of the California Department of Public Health) and cancer diagnosis records from 1988-2011 (collected by the California Cancer Registry). Histologically confirmed cases of pediatric HL (aged 0-19 years at the time of diagnoses) were identified using information reported to the California Cancer Registry. For each case, up to four controls were randomly sampled from statewide birth records and individually matched to each case on birth month and year, sex, and race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, Asian/Pacific Islander, and other). Record linkage and the selection of cases and controls were performed by research staff at the California Cancer Registry. The study protocol was approved by the Institutional Review Boards of California Health and Human Services and all participating academic institutions (Yale University, University of California, Berkeley, and University of California, San Francisco).

Study Population

The initial study population consisted of 1,323 pediatric HL cases and 5,292 matched controls. In order to preserve data quality, we excluded individuals with missing or unknown values for at least one of the following variables: birth weight, birth order, maternal age at the time of delivery, maternal birthplace, and delivery method (vaginal or cesarean). As a result, a total of 7 cases and 78 controls were excluded. We further excluded individuals (100 cases and 729 controls) with values that were outside of plausible ranges for birth weight (350g – 5,999g) and/or gestational age (20 – 44 weeks). As cases and controls were individually matched, any case without matched control, or vice versa, was excluded. This resulted in a final study population which consisted of 1,216 pediatric HL cases and 4,485 matched controls.

Variables of Interest

Data on birth weight, as well as various other infant, maternal, and paternal characteristics were obtained from birth records. We considered the following variables as potential confounders of the relation between birth weight and risk of pediatric HL: gestational age, birth order, plurality, maternal age at delivery, maternal birthplace, maternal education level, paternal age at delivery, paternal education level, delivery method, maternal history of diabetes, maternal history of pregnancy loss (defined as history of miscarriage and/or stillbirth), and proportion of the population living in poverty in the zip code of the mother's residence at time of delivery (as a proxy for socioeconomic status). Additional information about the diagnosis of pediatric HL, such as age at diagnosis and histological subtype, was obtained from the California Cancer Registry.

Statistical Analysis

Infant and parental characteristics were categorized and compared between cases and controls using Pearson's Chi-square test. To evaluate the association between birth weight and risk of pediatric HL, multivariable conditional logistic regression models (conditioned on matching factors of sex, race/ethnicity, and month/year of birth) were used to estimate odds ratios (ORs) and 95% confidence intervals (CIs). We examined birth weight, the primary exposure of interest, as both a categorical and continuous variable. For categorical analysis, birth weights were defined as low birth weight (<2,500g), normal birth weight (2,500g – 3,999g), and high birth weight (≥4,000g). For the multivariable analysis, the initial model included gestational age (20-36 weeks, 37-41 weeks, and 42-44 weeks), birth order (1st, 2nd, and 3rd or higher), plurality (singleton versus multiple birth), maternal age the time of delivery (<20, 20-24, 25-29, 30-34, and ≥35 years), maternal birthplace (foreign- versus US-born), maternal education level (12th grade or less, more than 12th grade, and unknown), paternal age at the time of delivery (<20, 20-24, 25-29, 30-34, ≥35 years, and unknown), paternal education level (12th grade or less, more than 12th grade, and unknown), delivery method (vaginal or cesarean), maternal history of diabetes, maternal history of pregnancy loss, and the proportion of the population living in poverty within the zip code of the mother's residence at the time of delivery (<5%, 5-9%, 10-19%, ≥20%, and unknown). After a stepwise selection, the final model evaluating the association between birth weight and risk of overall pediatric HL adjusted for birth order, maternal age at the time of delivery, and paternal age at the time of delivery.

We further evaluated the relationship between birth weight and risk of pediatric HL by age at diagnosis (0-10, 0-14, 11-14, and 15-19 years), histological subtype, and race/ethnicity.

Within each subgroup, covariates in the final models were also obtained using stepwise selection procedures.

We also conducted a sensitivity analysis in which unconditional logistic regression models were performed that included the matching factors as well as all other covariates described above. All significance tests were two-sided with an α-level of 0.05. All analyses were conducted using SAS, version 9.4 (SAS Institute, Inc., Cary, North Carolina).

Results

Of the 1,216 pediatric HL cases included in the study, a majority (55.8%) were male, and 53.4% were diagnosed at 15-19 years of age (Table 1, Figure 1). Based on unadjusted associations, cases and controls were significantly different with respect to birth weight (p=0.01). Cases appeared to have a higher birth weight than controls, with 14.8% of cases having a high birth weight compared to 12.1% of controls, and 4.3% of cases presenting a low birth weight compared to 5.6% of controls. Cases and controls were also significantly different with respect to maternal age at the time of delivery (p<0.01) and paternal age at the time of delivery (p<0.01). At the time of delivery, parents of cases were older than parents of controls. Cases and controls also differed with respect to delivery method (p=0.04). Cases were more likely to be delivered by cesarean section (24.9% for cases compared to 22.1% for controls). The remaining characteristics were similar between cases and controls (Table 1).

Based on the final multivariable conditional logistic regression model (Table 2), compared to normal birth weight, high birth weight was positively associated with risk of pediatric HL (OR=1.23, 95% CI: 1.02-1.48; p=0.03). Low birth weight showed a nonsignificant protective effect against risk of pediatric HL (OR=0.79, 95% CI: 0.58-1.07; p=0.13). When birth

weight was modelled continuously, a 1,000g increase in birth weight was associated with a 16% increase in risk of pediatric HL (95% CI: 1.03-1.30; p=0.01). Compared with first born children, children who were third or higher in birth order had significantly reduced risk of pediatric HL (OR=0.80, 95% CI: 0.67-0.95; p=0.01). There was also suggestion that younger parental age was associated with reduced risk of pediatric HL in the overall study population (Table 2).

In further analyses evaluating the relationship between birth weight and pediatric HL by age of diagnosis (Tables 2-3, Figure 2), significant positive associations for high birth weight and risk of HL were observed among those diagnosed at 0-10 years (OR=1.56, 95% CI: 1.04-2.34; p=0.03), or 15-19 years (OR=1.43, 95% CI: 1.11-1.83; p<0.01). There was no significant association between birth weight and risk of HL diagnosed at the ages of 0-14 years or 11-14 years. Within the age group of 15-19 years, low birth weight was significantly associated with a 44% decrease in odds of HL (OR=0.56, 95% CI: 0.36-0.89; p=0.01), an association which was absent in the overall study population (Tables 2-3). In addition, the association between birth order and risk of HL also varied by age of diagnosis, in that a significant association was observed among those diagnosed at 15-19 years (OR=0.66, 95% CI: 0.52-0.84; p<0.01), but not among those diagnosed at 0-14 years (Table 2).

Additional stratified analyses by histological subtype and race/ethnicity revealed that high birth weight was significantly associated with increased disease risk among cases with the subtype of nodular sclerosis (OR=1.26, 95% CI: 1.02-1.57; p=0.03), but not among other subgroups (Table 3). Results from the sensitivity analysis using unconditional logistic regression were consistent with the findings from conditional logistic regression models (detailed data not presented).

Discussion

In this large population-based study, we found that high birth weight was associated with an increased risk of pediatric HL. Additionally, birth order was associated with risk of pediatric HL, and having a birth order of third or higher (compared to being the first born child) conferred a significant protective effect. However these effects were not consistent across subgroups defined by age of diagnosis, histological subtype, and race/ethnicity.

For high birth weight and risk of pediatric HL, the magnitude of association was stronger in certain subgroups defined by age (0-10 years and 15-19 years), but it was absent in others (0-14 years and 11-14 years). Similarly, across subgroups, third or higher birth order (compared to first born) was only associated with decreased disease risk among cases diagnosed at 15-19 years of age. It is not clear why these associations were not consistent across subgroups, but it is possible that HL diagnosed at different ages may have distinct etiology. HL incidence varies by age, following a bimodal age distribution with peaks between 15-34 years and greater than 60 years,[14] and it has been proposed that age of diagnosis may be associated with the etiologic profile of HL.[15]

A majority of cases in our study population were classified as nodular sclerosis based on histology, and the relationship between birth weight and risk of pediatric HL in this subgroup mirrored the results from the overall population. As the histological subtype of mixed cellularity is much rarer, we were unable to assess whether the apparent absence of association between birth weight and this subtype was due to small sample size and limited power, or any possible difference in etiology.

Although high birth weight has been implicated as a risk factor for several other types of pediatric cancer, such as leukemia, neuroblastoma, brain tumors (astrocytoma and

medulloblastoma), and Wilms' tumor,[16-20] the role of birth weight in the etiology of pediatric HL is not as clear. The positive association between high birth weight and risk of HL had previously been reported to be similar in cases diagnosed at 0-14 years and 15-37 years.[13] Milne et al. utilized proportion of optimal birth weight (POBW) as a metric for appropriateness of fetal growth[21] and found that a higher POBW was associated with an increased risk of childhood HL (age 0-14 years) in boys.[22] Aside from these studies, the majority of previously published studies that have evaluated birth weight and risk of HL in pediatric populations have reported null findings,[4-12] and most of those studies included only cases diagnosed at the age of 0-14 years.[4-6,8,10,11] When we restricted our cases to those diagnosed at the age of 0-14 years, we also observed a similar null finding. In future epidemiological research of pediatric HL, it is probably important to consider age of diagnosis as a potential marker for distinct underlying etiology.

Our results pointed to a decreased risk of pediatric HL for those with a birth order of third or higher. A study which evaluated HL risk in a young adult population (aged 15-39 years at the time of diagnosis) identified a protective effect for higher birth order in which those born fourth or later in their family had reduced risk of HL (relative to those born third or earlier).[23] Another study reported significantly different risk patterns for birth order between childhood (<15 years) and young adult (≥15 years) populations, such that higher birth order appeared to decrease risk of HL in the young adult population and (non-significantly) increase risk of HL in children under 15 years.[24] These differing risk patterns for birth order and risk of HL between childhood and young adult populations are particularly noteworthy in the context our results. Although higher birth order corresponded to decreased HL risk in our overall study population (0-19 years), subgroup analyses revealed that birth order was only a significant predictor in the aged 15-19 years population. As such, the effect of birth order on risk of HL may be modified by age at

diagnosis. Alternatively, a higher incidence of HL in the age group of 15-19 years may simply offer an improved statistical power to detect an association, if one truly exists.

Our study has several important strengths. Population-based record linkage in a state as populous as California gave rise to a large number of pediatric HL cases relative to earlier studies, and presented a significant advantage in terms of statistical power. A record-based study without the need to trace or consent any subjects minimized concerns of selection bias. Additionally, data on exposure of interest, potential confounders, and disease outcome were obtained exclusively from preexisting records, which minimized any potential for recall bias.

In light of these noted advantages, there were also limitations to our study. In particular, we were limited to data available in existing records, and therefore could not adjust for additional possible risk factors for pediatric HL such as maternal smoking during pregnancy[25] and history of Epstein-Barr virus (EBV) infection or infectious mononucleosis.[26,27] Nevertheless, a recent study conducted by the Children's Oncology Group reported that fewer than 24% of childhood HL cases had EBV-positive tumor, and there did not appear to be systematic differences in risk factors by EBV status.[28] In addition, we did adjust for a number of other potential confounder based on information contained in birth records, and we excluded individuals with missing or improbable values for important variables in order to ensure high data quality. Finally, it is possible that some cases were not captured by the California Cancer Registry as a result of moving out of California or incomplete case ascertainment, and some control patients may have been misclassified. However, under the extreme assumption that all controls were lost to follow-up, based on the age-adjusted incidence rates of pediatric HL (age 0-19 years) for the United States over the study period,[2] only fewer than two incident cases of HL would have arisen from

the 4,485 controls, had they been followed through their 20th birthday. As such, the potential for bias due to misclassification of the disease outcome was minimal.

In conclusion, this study provides evidence for a positive association between high birth weight and risk of pediatric HL. The different findings by age of diagnosis with regard to both birth weight and birth order suggest that it may be important to stratify pediatric HL by age at diagnosis for future etiological investigations.

References

1. Ward E, DeSantis C, Robbins A, Kohler B, Jemal A. Childhood and adolescent cancer statistics, 2014. CA: A Cancer Journal for Clinicians 2014;64:83-103.

2. Howlader N, Noone A, Krapcho M, et al. SEER cancer statistics review, 1975–2013. Bethesda, MD: National Cancer Institute 2016.

3. Castellino SM, Geiger AM, Mertens AC, et al. Morbidity and mortality in long-term survivors of Hodgkin lymphoma: a report from the Childhood Cancer Survivor Study. Blood 2011;117:1806-16.

4. Spector LG, Puumala SE, Carozza SE, et al. Cancer risk among children with very low birth weights. Pediatrics 2009;124:96-104.

5. Smith A, Lightfoot T, Simpson J, Roman E. Birth weight, sex and childhood cancer: a report from the United Kingdom Childhood Cancer Study. Cancer Epidemiology 2009;33:363-7.

6. Roman E, Simpson J, Ansell P, et al. Perinatal and reproductive factors: a report on haematological malignancies from the UKCCS. European Journal of Cancer 2005;41:749-59.

7. Yeazel MW, Ross JA, Buckley JD, Woods WG, Ruccione K, Robison LL. High birth weight and risk of specific childhood cancers: a report from the Children's Cancer Group. The Journal of Pediatrics 1997;131:671-7.

8. Petridou ET, Dikalioti SK, Skalkidou A, Andrie E, Dessypris N, Trichopoulos D. Sun exposure, birth weight, and childhood lymphomas: a case control study in Greece. Cancer Causes & Control 2007;18:1031-7.

9. Marcotte EL, Ritz B, Cockburn M, Clarke CA, Heck JE. Birth characteristics and risk of lymphoma in young children. Cancer Epidemiology 2014;38:48-55.

10. Petridou ET, Sergentanis TN, Skalkidou A, et al. Maternal and birth anthropometric characteristics in relation to the risk of childhood lymphomas: a Swedish nationwide cohort study. Eur J Cancer Prev 2015;24:535-41.

11. O'Neill KA, Murphy MF, Bunch KJ, et al. Infant birthweight and risk of childhood cancer: international population-based case control studies of 40 000 cases. International Journal of Epidemiology 2015;44:153-68.

12. Papadopoulou C, Antonopoulos C, Sergentanis T, Panagopoulou P, Belechri M, Petridou E. Is birth weight associated with childhood lymphoma? A meta-analysis. International Journal of Cancer 2012;130:179-89.

13. Crump C, Sundquist K, Sieh W, Winkleby MA, Sundquist J. Perinatal and Family Risk Factors for Hodgkin Lymphoma in Childhood Through Young Adulthood. American Journal of Epidemiology 2012;176:1147-58.

14. Nakatsuka S-i, Aozasa K. Epidemiology and pathologic features of Hodgkin lymphoma. International journal of hematology 2006;83:391-7.

15. Jarrett R. Viruses and Hodgkin's lymphoma. Annals of Oncology 2002;13:23-9.

16. Caughey RW, Michels KB. Birth weight and childhood leukemia: A meta-analysis and review of the current evidence. International Journal of Cancer 2009;124:2658-70.

17. Daling JR, Starzyk P, Olshan AF, Weiss NS. Birth Weight and the Incidence of Childhood Cancer. Journal of the National Cancer Institute 1984;72:1039-41.

18. Harder T, Plagemann A, Harder A. Birth weight and risk of neuroblastoma: a meta-analysis. International Journal of Epidemiology 2010;39:746-56.

19. Harder T, Plagemann A, Harder A. Birth weight and subsequent risk of childhood primary brain tumors: a meta-analysis. American Journal of Epidemiology 2008;168:366-73.

20. Chu A, Heck JE, Ribeiro KB, et al. Wilms' tumour: a systematic review of risk factors and meta-analysis. Paediatric and Perinatal Epidemiology 2010;24:449-69.

21. Blair EM, Liu Y, de Klerk NH, Lawrence DM. Optimal fetal growth for the Caucasian singleton and assessment of appropriateness of fetal growth: an analysis of a total population perinatal database. BMC Pediatrics 2005;5:1.

22. Milne E, Laurvick CL, Blair E, de Klerk N, Charles AK, Bower C. Fetal growth and the risk of childhood CNS tumors and lymphomas in Western Australia. International Journal of Cancer 2008;123:436-43.

23. Gutensohn N, Cole P. Childhood social environment and Hodgkin's disease. New England Journal of Medicine 1981;304:135-40.

24. Westergaard T, Melbye M, Pedersen JB, Frisch M, Olsen JH, Andersen PK. Birth order, sibship size and risk of Hodgkin's disease in children and young adults: a population-based study of 31 million person-years. International Journal of Cancer 1997;72:977-81.

25. Antonopoulos C, Sergentanis T, Papadopoulou C, et al. Maternal smoking during pregnancy and childhood lymphoma: A meta-analysis. International Journal of Cancer 2011;129:2694-703.

26. Hjalgrim H, Askling J, Sørensen P, et al. Risk of Hodgkin's Disease and Other Cancers After Infectious Mononucleosis. Journal of the National Cancer Institute 2000;92:1522-8.

27. Hjalgrim H, Askling J, Rostgaard K, et al. Characteristics of Hodgkin's Lymphoma after Infectious Mononucleosis. New England Journal of Medicine 2003;349:1324-32.

28. Linabery AM, Erhardt EB, Richardson MR, et al. Family history of cancer and risk of pediatric and adolescent Hodgkin lymphoma: A Children's Oncology Group study. International Journal of Cancer 2015;137:2163-74.

Table 1: Infant, Maternal, and Paternal Characteristics of the Study Population

	Cases		Controls		
Characteristics	**n**	**(%)**	**n**	**(%)**	**p-value***
Total	1216		4485		
Sex					0.84
Female	537	(44.2)	1966	(43.8)	
Male	679	(55.8)	2519	(56.2)	
Race/ethnicity					1.00
Non-Hispanic white	562	(46.2)	2089	(46.6)	
Non-Hispanic black	99	(8.1)	362	(8.1)	
Hispanic	467	(38.4)	1713	(38.2)	
Asian/Pacific Islander	70	(5.8)	259	(5.8)	
Other	18	(1.5)	62	(1.4)	
Year of birth					0.72
1978-1982	245	(20.1)	840	(18.7)	
1983-1987	310	(25.5)	1145	(25.5)	
1988-1992	418	(34.4)	1579	(35.2)	
1993-2009	243	(20.0)	921	(20.5)	
Birth weight (in grams)					0.01
Low (<2500)	52	(4.3)	249	(5.6)	
Normal (2500-3999)	984	(80.9)	3694	(82.4)	
High (≥4000)	180	(14.8)	542	(12.1)	
Gestational age (in weeks)					0.51
20-36	101	(8.3)	416	(9.3)	
37-41	984	(80.9)	3568	(79.6)	
42-44	131	(10.8)	501	(11.2)	
Birth order					0.19
1st	483	(39.7)	1851	(41.3)	
2nd	409	(33.6)	1386	(30.9)	
3rd or higher	324	(26.6)	1248	(27.8)	
Plurality					0.17
Singleton	1186	(97.5)	4402	(98.1)	
Multiple	30	(2.5)	83	(1.9)	
Maternal age at delivery (in years)					<.01
<20	107	(8.8)	534	(11.9)	
20-24	265	(21.8)	1240	(27.6)	
25-29	400	(32.9)	1309	(29.2)	
30-34	303	(24.9)	951	(21.2)	
≥35	141	(11.6)	451	(10.1)	
Maternal education level					0.81
12th grade or less	375	(30.8)	1424	(31.8)	
More than 12th grade	242	(19.9)	892	(19.9)	
Unknown	599	(49.3)	2169	(48.4)	

Paternal age at delivery (in years)					<.01
<20	43	(3.5)	184	(4.1)	
20-24	170	(14.0)	903	(20.1)	
25-29	343	(28.2)	1208	(26.9)	
30-34	311	(25.6)	1122	(25.0)	
≥35	302	(24.8)	865	(19.3)	
Unknown	47	(3.9)	203	(4.5)	
Paternal education level					0.65
12th grade or less	341	(28.0)	1319	(29.4)	
More than 12th grade	242	(19.9)	873	(19.5)	
Unknown	633	(52.1)	2293	(51.1)	
Maternal birthplace					0.25
United States	799	(65.7)	3025	(67.4)	
Foreign	417	(34.3)	1460	(32.6)	
Delivery method					0.04
Vaginal	913	(75.1)	3494	(77.9)	
Cesarean	303	(24.9)	991	(22.1)	
Maternal diabetes					0.61
No	1207	(99.3)	4445	(99.1)	
Yes	9	(0.7)	40	(0.9)	
History of pregnancy loss					0.23
No	994	(81.7)	3719	(82.9)	
Yes	221	(18.2)	753	(16.8)	
Unknown	1	(0.1)	13	(0.3)	
% population living in poverty (by zip code)					0.53
<5%	154	(12.7)	519	(11.6)	
5-9%	259	(21.3)	1035	(23.1)	
10-19%	372	(30.6)	1327	(29.6)	
≥20%	215	(17.7)	832	(18.6)	
Unknown	216	(17.8)	772	(17.2)	

*P-values were calculated using Pearson's Chi-square test

Column percent totals may not sum to 100% due to rounding

Table 2: Factors associated with risk of pediatric Hodgkin lymphoma

Characteristics	OR*	(95% CI)*	p-value
Overall; ages 0-19 years (1216 cases/4485 controls)			
Birth weight (in grams)			
Low (<2500)	0.79	(0.58, 1.07)	0.13
Normal (2500-3999)	1.00	(Reference)	
High (≥4000)	1.23	(1.02, 1.48)	0.03
Per 1,000g increase	1.16	(1.03, 1.30)	0.01
Birth order			
1st	1.00	(Reference)	
2nd	1.02	(0.87, 1.19)	0.79
3rd or higher	0.80	(0.67, 0.95)	0.01
Maternal age at delivery (in years)			
<20	0.66	(0.48, 0.89)	<0.01
20-24	0.73	(0.60, 0.88)	<0.01
25-29	1.00	(Reference)	
30-34	1.03	(0.86, 1.24)	0.76
≥35	0.94	(0.73, 1.21)	0.63
Paternal age at delivery (in years)			
<20	0.99	(0.66, 1.51)	0.98
20-24	0.76	(0.61, 0.95)	0.02
25-29	1.00	(Reference)	
30-34	0.94	(0.78, 1.14)	0.54
≥35	1.22	(0.98, 1.52)	0.08
Unknown	0.90	(0.63, 1.28)	0.56
Ages 0-14 years (567 cases/2100 controls)			
Birth weight (in grams)			
Low (<2500)	1.10	(0.72, 1.70)	0.66
Normal (2500-3999)	1.00	(Reference)	
High (≥4000)	1.07	(0.81, 1.42)	0.62
Per 1,000g increase	1.01	(0.85, 1.20)	0.93
Maternal age at delivery (in years)			
<20	0.81	(0.59, 1.13)	0.21
20-24	0.74	(0.57, 0.96)	0.02
25-29	1.00	(Reference)	
30-34	1.02	(0.79, 1.32)	0.88
≥35	1.00	(0.73, 1.38)	1.00
Maternal birthplace			
United States	1.00	(Reference)	
Foreign	1.28	(1.01, 1.62)	0.04

Ages 15-19 years (649 cases/2385 controls)

Birth weight (in grams)			
Low (<2500)	0.56	(0.36, 0.89)	0.01
Normal (2500-3999)	1.00	(Reference)	
High (≥4000)	1.43	(1.11, 1.83)	<0.01
Per 1,000g increase	1.33	(1.13, 1.57)	<0.01
Birth order			
1st	1.00	(Reference)	
2nd	0.96	(0.77, 1.19)	0.69
3rd or higher	0.66	(0.52, 0.84)	<0.01
Maternal age at delivery (in years)			
<20	0.48	(0.30, 0.76)	<0.01
20-24	0.67	(0.51, 0.87)	<0.01
25-29	1.00	(Reference)	
30-34	1.01	(0.78, 1.31)	0.93
≥35	0.90	(0.63, 1.29)	0.57
Maternal education level			
12th grade or less	1.00	(Reference)	
More than 12th grade	0.90	(0.67, 1.23)	0.51
Unknown	1.23	(0.37, 4.06)	0.74
Paternal age at delivery (in years)			
<20	0.99	(0.51, 1.93)	0.98
20-24	0.69	(0.51, 0.95)	0.02
25-29	1.00	(Reference)	
30-34	0.93	(0.72, 1.20)	0.57
≥35	1.37	(1.02, 1.84)	0.04
Unknown	0.72	(0.41, 1.25)	0.24
% population living in poverty (by zip code)			
<5%	1.30	(0.97, 1.75)	0.08
5-9%	0.84	(0.64, 1.09)	0.18
10-19%	1.00	(Reference)	
≥20%	1.01	(0.76, 1.35)	0.94
Unknown	0.82	(0.47, 1.44)	0.49

*Odds ratios (OR) were derived from multivariable stepwise conditional logistic regression; all variables in the model were mutually adjusted for each other; CI = confidence interval.

Table 3: Birth weight and risk of pediatric Hodgkin lymphoma by age of diagnosis, histological subtype, and race/ethnicity

		Birth weight (in grams)				
		Low (<2500)		Normal (2500-3999)	High (≥4000)	
Group	**Cases/controls**	**OR (95% CI)***	**p-value**		**OR (95% CI)***	**p-value**
Overall (0-19 years)[a]	1216/4485	0.79 (0.58, 1.07)	0.13	1.00 (reference)	1.23 (1.02, 1.48)	0.03
Age at Diagnosis						
0-10 years[b]	241 /904	0.64 (0.28, 1.44)	0.28	1.00 (reference)	1.56 (1.04, 2.34)	0.03
0-14 years[c]	567 /2100	1.10 (0.72, 1.70)	0.66	1.00 (reference)	1.07 (0.81, 1.42)	0.62
11-14 years[d]	326 /1196	1.40 (0.83, 2.37)	0.21	1.00 (reference)	0.81 (0.55, 1.20)	0.30
15-19 years[e]	649 /2385	0.56 (0.36, 0.89)	0.01	1.00 (reference)	1.43 (1.11, 1.83)	<0.01
Histological Subtype						
Nodular sclerosis[f]	883 /3259	0.73 (0.50, 1.06)	0.10	1.00 (reference)	1.26 (1.02, 1.57)	0.03
Mixed cellularity[g]	124 /464	0.88 (0.33, 2.36)	0.80	1.00 (reference)	0.85 (0.46, 1.58)	0.61
Race/Ethnicity						
Non-Hispanic white[h]	562 /2089	0.46 (0.24, 0.89)	0.02	1.00 (reference)	1.27 (0.98, 1.64)	0.07
Hispanic[i]	467 /1713	1.15 (0.72, 1.83)	0.56	1.00 (reference)	1.19 (0.87, 1.63)	0.27

*Abbreviations: CI, confidence interval; OR, odds ratio.

[a]Adjusted for birth order, maternal age at delivery, and paternal age at delivery.

[b]Adjusted for maternal education level.

[c]Adjusted for maternal age at delivery and maternal birthplace.

[d]Adjusted for maternal birthplace, and % population living in poverty (by zip code).

[e]Adjusted for birth order, maternal age at delivery, maternal education level, paternal age at delivery, and % population living in poverty (by zip code).

[f]Adjusted for paternal age at delivery, delivery method, and % population living in poverty (by zip code).

[g]Unadjusted (no significant predictors remained after stepwise regression).

[h]Adjusted for gestational age, maternal age at delivery, paternal age at delivery, maternal birthplace and % population living in poverty (by zip code).

[i]Adjusted for birth order and paternal age.

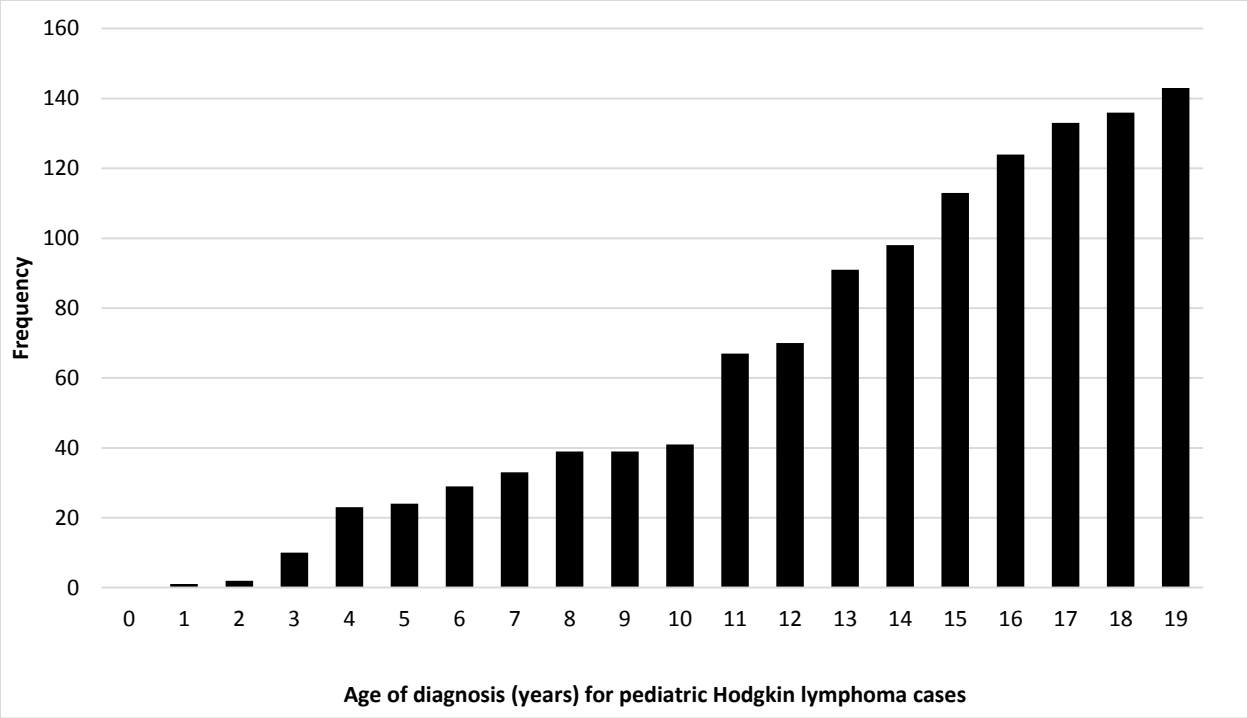

Figure 1: Age of cases at the time of diagnosis

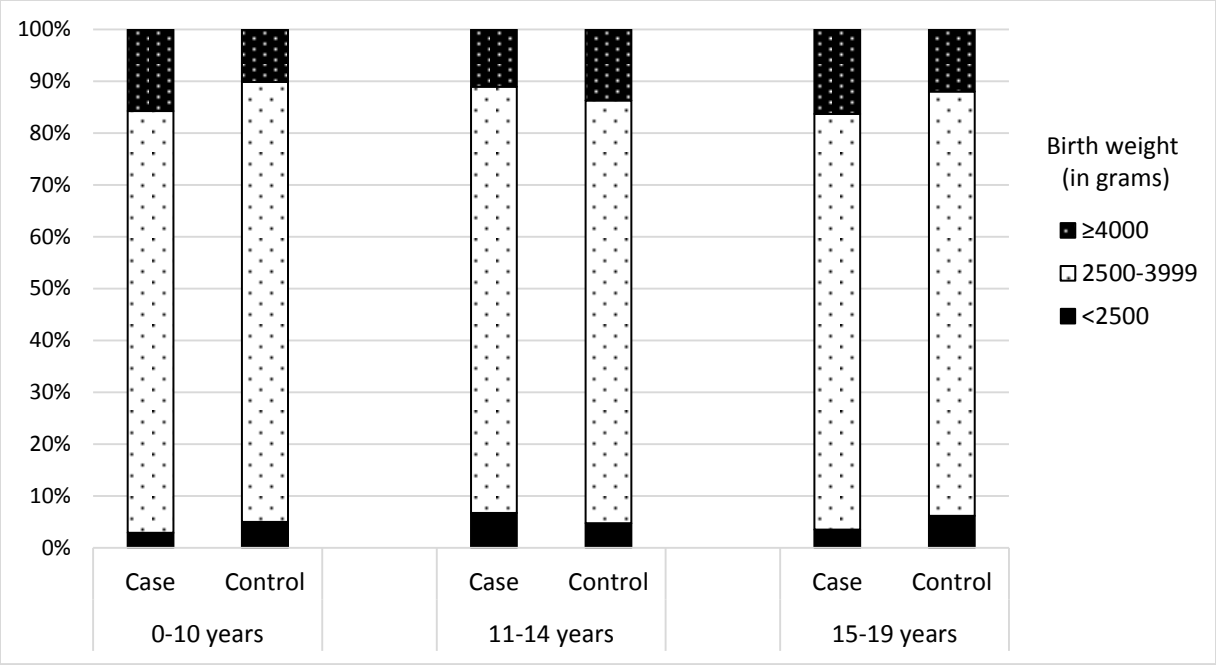

Figure 2: Birth weight by case/control status across subgroups defined by age